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# Regulation of the renal circulation

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It is a great pleasure for me to participate in honoring my mentor, Dr. Donald W. Seldin. When I began my fellowship in Dallas in 1967, the field of renal physiology was booming. Laboratories all over the world were beginning to unravel the puzzle of sodium handling by the nephron and Seldin was one of the main catalysts. From this intellectual experience in Dallas, I spent the next decade or so studying the renal circulation, its effect on sodium transport, and various humoral factors that play a role in the regulation of renal resistance. It's incredible how much our knowledge has changed in these 23 years. I first heard of prostaglandins in 1968 at one of the weekly sessions in Dallas from a visiting professor. Renal autoregulation was poorly understood and few incisive experimental studies had been done. The kinin system was just beginning to emerge and obviously no one had heard of atrial natriuretic peptide or endothelin.

In this brief article, I'd like to review two facets of the renal circulation: autoregulation and various humoral agents which regulate renal vasomotor tone. Because of space constraints, this will be quite brief and I would refer interested readers to a more extensive review of the subject by Dr. Claudia Hura and myself [1].

## Autoregulation

In the past 15 to 20 years, various researchers beginning with Brenner and his group, have quantified segmental vascular resistance in the steady state and during various experimental maneuvers such as a reduction in renal perfusion pressure [2]. Most of our information on renal vascular resistance comes from micropuncture data in dogs and rats. Hydrostatic pressure decreases by a finite and significant amount between the renal artery and glomerular capillaries. This pressure drop was initially presumed to be due primarily to resistance changes in the afferent arteriole. In the anesthetized rat, afferent arteriolar resistance has been reported to be responsible for 60% of the total renal vascular resistance [3, 4]. Data from the dog is more variable, suggesting that the afferent arteriolar contribution to total renal vascular resistance varies from 40 to 60% [5, 6]. There is also recent evidence in the rat to suggest that the interlobular artery may contribute a significant amount to preglomerular vascular resistance [7]. These studies suggest that vessels proximal to the afferent arteriole contribute 26% of the total renal vascular resistance. This has not been found to be true in the dog [8]. Data obtained from the rat suggests that efferent arteriolar resistance constitutes approximately 30% of total renal vascular resistance [3, 4, 9, 10]. With these basic data, let's now turn to autoregulation.

It appears that renal blood flow autoregulation is mediated primarily by resistance changes in the afferent arteriole [4]. Efferent arteriolar resistance changes little until perfusion pressure falls below 80 mm Hg. These renal vascular autoregulatory changes occur within one second of the change in perfusion pressure and are usually complete within 15 to 20 seconds [11].

Currently, there are two mechanisms which may explain renal autoregulation. They are the distal tubular feedback hypothesis (tubuloglomerular feedback) and the myogenic hypothesis.

### *Distal tubular feedback hypothesis*

Originally described by Thurau and Schnermann, the distal tubular feedback hypothesis or tubuloglomerular feedback relates the composition of distal tubular fluid to changes in renal vascular resistance and glomerular filtration rate in that particular nephron [12]. However, the majority of studies indicate that tubuloglomerular feedback is not the mechanism responsible for renal blood flow autoregulation.

For example, Kallskog et al studied interlobular arteries that reached the surface of the rat kidney and found that these vessels were capable of autoregulation when perfusion pressure was decreased [13]. The authors concluded that since the macula densa was not anatomically related to the interlobular artery, it was unlikely that a distal tubular feedback mechanism was responsible for autoregulatory behavior at least in this species. Further, Young and Marsh evaluated the time course of autoregulation following rapid changes in renal perfusion pressure [11]. They found that autoregulatory changes occurred before the changes in distal tubular fluid composition could occur. Thus, other mechanisms must exist to explain renal blood flow autoregulation.

### *Myogenic theory*

This theory was originally proposed by Bayliss based on blood flow autoregulatory studies in the dog and cat hind limb [14]. LaPlace's law states that $T = R(P_V - P_{EV})$ where T is the wall tension, R is the vessel radius, $P_V$ is the intravascular hydraulic pressure and $P_{EV}$ is the extravascular hydraulic pressure. Assuming that vessel wall tension is to be maintained constant, changes in transmural pressure would result in inverse changes in vessel radius.

A number of findings support a role for the myogenic theory in renal autoregulation. First, infusion of papaverine which

caused smooth muscle paralysis, abolishes autoregulation [15]. Second, the rapidity of vascular resistance changes after changes in renal perfusion pressure (one to three seconds) is compatible with a myogenic response.

Studies by Gilmore et al on renal tissue transplanted to the hamster cheek pouch provide direct evidence for myogenic autoregulation [16]. A rise in chamber pressure resulted in increased cheek pouch interstitial pressure and an increase in afferent arteriolar radius. Interstitial pressure changes had no effect on the efferent arteriole. Finally, Edwards studied isolated afferent and efferent arterioles of the rabbit [17]. Afferent arterioles exhibited appropriate autoregulatory behavior in response to incremental changes in intravascular pressure, while efferent arterioles did not. Thus, current data would seem to indicate that renal blood flow autoregulation is mediated primarily by an intrinsic myogenic mechanism at the level of the afferent arteriole.

## Vasoactive substances

### *Renin-angiotensin system (RAS)*

Exogenous infusions of angiotensin II (Ang II) have been shown to decrease renal blood flow in both man [18] and experimental animals [19, 20]. Glomerular filtration rate is reduced, but to a lesser extent resulting in an increase in the filtration fraction [21, 22]. Micropuncture studies employing exogenous administration of Ang II have demonstrated reduction in glomerular plasma flow and single nephron glomerular filtration rate [23, 24]. Studies in the rat have shown an Ang II-induced decrease in the ultrafiltration coefficient [23].

Experimental efforts have also concentrated on the study of the renin-angiotensin system as a local regulatory system and on the possibility that intrarenally formed Ang II acts to modulate renal vascular tone. Studies using immunohistochemical techniques have confirmed the intrarenal location of the components of the renin-angiotensin system [25, 26]. The substantial quantity of angiotensin converting enzyme present in interstitial and intravascular locations in the kidney could convert both intrarenally generated Ang I and systemically delivered Ang I to Ang II [27, 28]. Various techniques have estimated the intrarenal conversion rate of systemically delivered Ang I to Ang II to be between 1 and 20% [29–31]. Measured Ang II concentrations in renal lymph are over 100 times greater than plasma levels [32] and approximately 10-fold higher than in renal blood [33, 34]. These data suggest the kidney is capable of synthesizing Ang II in quantities sufficient to have local effects on renal hemodynamics.

The effects of the intrarenal RAS has been investigated using several techniques. Converting enzyme inhibitors have been infused intrarenally to block the formation of endogenous Ang II. The response observed in the kidney is dependent on the pre-existing level of activation of the RAS. Thus, to maximize the renal response to angiotensin blockade, prior activation of the RAS has been experimentally achieved using a low sodium diet or a reduction of renal artery pressure. There seems to be general agreement that in such models where the renin-angiotensin system has been previously activated, Ang II blockade results in an increase in renal blood flow [35–37].

The controversy regarding the role of Ang II in renal blood flow autoregulation has been studied in many laboratories. The majority of experimental data using infusions of Ang II, infusions of Ang II antagonists, or chronic renin depletion models have not supported a role for the renin-angiotensin system in the autoregulation of renal blood flow [38–40].

Micropuncture studies in dogs and rats have also suggested that Ang II is capable of both afferent and efferent arteriolar vasoconstriction [23, 37]. In the split hydronephrotic kidney preparation, Ang II infusion caused vasoconstriction of both afferent and efferent arterioles [41, 42]. Both afferent and efferent vasoconstriction in response to Ang II was also demonstrated in the blood-perfused juxtamedullary nephron preparation [43]. In isolated rabbit afferent and efferent arterioles statically perfused in vitro, Ang II produced only efferent vasoconstriction with no apparent effect on the afferent arteriole [17].

Some of the conflicting data regarding the influence of Ang II on segmental vascular resistance in the kidney needs to be interpreted in view of the multiple potential interactions between Ang II and other vasoactive and hormonal systems. Ang II is felt to enhance adrenergic activity by increasing norepinephrine release at the neuroeffector junction [44, 45]. Conversely, renal nerve stimulation increases the release of renin by the kidney [46].

Recent studies have also suggested an interaction between Ang II and adenosine in controlling afferent arteriolar resistance. The studies indicate that the presence of Ang II is necessary for adenosine-induced renal vasoconstriction [47]. Conversely, high levels of adenosine may alter the responsiveness of afferent arterioles to Ang II by uncovering a potent constrictor response to Ang II [48]. Finally, vasodilatory prostaglandins may act to modify the renal vascular response to Ang II.

In summary, currently available data suggest that both endogenous and exogenous Ang II influence renal hemodynamics. While Ang II has been clearly shown to be capable of causing vasoconstriction in afferent arterioles, its primary physiologic action appears to be on the efferent arteriole.

### *Vasopressin*

Vasopressin may play a role in the control of renal blood flow but the magnitude and direction of its influence is unclear. Exogenous infusion of vasopressin in low doses has been reported to cause an increase in renal blood flow [49]. The intrarenal administration of high dose AVP (approximately 20 ng/kg/min) has produced renal vasoconstriction and a decline in renal blood flow in some studies [50, 51], while other investigators have failed to demonstrate any effects on total renal blood flow [52]. The reason for these conflicting results is unclear, but may be due in part to varying doses of vasopressin, varying states of fluid balance in the animals used, and the influence of other modulating vasoactive agents, such as prostaglandins.

The influence of vasopressin on regional renal blood flow has been examined. It was proposed that since increased medullary blood flow tends to wash out solute from the medulla, a decrease in medullary blood flow should increase renal concentrating ability. Therefore, ADH could augment medullary tonicity by selectively reducing medullary blood flow. This hypothesis was initially supported by a number of studies [53, 54].

The most recent examination of the question by Zimmer-

hackl, Robertson and Jamison has employed the videomicroscopic technique and specific $V_1$ and $V_2$ receptor antagonists in the rat [55]. In these studies, the transition from diuresis to antidiuresis was associated with a decrease in medullary blood flow. Infusion of physiologic doses of AVP resulted in vasoconstriction of the vasa recta which was partially blocked by a $V_1$ receptor antagonist. Administration of a $V_2$ antagonist restored medullary blood flow to values seen in water diuresis. Selective inhibition of AVP-induced papillary vasoconstriction with a $V_1$ receptor antagonist did not influence urinary concentrating ability. Thus, it would seem that the effects of AVP on medullary blood flow are not necessary for its antidiuretic effect and may be a consequence rather that the cause of alterations in urinary concentrating and diluting mechanisms.

### *Adenosine*

Adenosine, a nucleoside product of adenosine triphosphate (ATP) hydrolysis is felt to play a role in the control of renal blood flow and glomerular filtration [56].

The intrarenal infusion of adenosine produces a short-lived, dose-related reduction in renal blood flow of approximately one to four minutes duration. This is followed by a return to baseline or slightly elevated levels of blood flow [47, 56]. When the adenosine infusion is stopped, blood flow rate may transiently increase even further [57]. Chronic administration of adenosine over a period of days to conscious dogs results in a dose-related vasodilation [58]. Glomerular filtration rate and filtration fraction are decreased for the duration of adenosine infusion, regardless of the effect on total renal blood flow.

The effects of adenosine on the renal microcirculation have also been examined. Tagawa and Vander calculated arteriolar resistance changes in dogs receiving intrarenal adenosine infusions and reported afferent arteriolar vasoconstriction and efferent arteriolar vasodilation [59]. Micropuncture studies performed in dogs during intrarenal adenosine infusion demonstrated vasoconstriction of superficial cortical afferent arterioles at a time when total renal blood flow had stabilized [57]. However, Hall, Granger and Hester calculated serial changes in vascular resistance and demonstrated an initial increase in afferent arteriolar resistance which fell to control levels as total renal blood flow returned to or exceeded baseline values [47]. In isolated canine afferent arterioles statically perfused in vitro, 2-chloroadenosine, a non-selective, nonmetabolized adenosine analog, produced short-lived vasoconstriction of 3 to 10 minutes duration despite continued presence of the 2-chloradenosine [60]. No change in the glomerular ultrafiltration coefficient has been noted with adenosine infusion [57].

Arend, Thompson and Spielman studied the effects of dipyridamole, an adenosine uptake blocker [61]. They demonstrated that dipyridamole administration elevated renal adenosine levels, and that GFR declined in sodium-depleted but not sodium-loaded dogs. This decline in GFR was inhibited by theophylline. Hall and colleagues found that infusion of the converting enzyme inhibitor SQ14225 almost completely abolished adenosine-mediated vasoconstriction, while infusion of angiotensin II restored the vasoconstrictor response to adenosine in dogs treated with SQ14225 [47]. When angiotensin is infused with adenosine, the initial vasoconstrictor response is prolonged. Afferent arteriolar resistance remains elevated during the entire infusion, however, despite the return of renal blood flow to normal [48]. Adenosine may alter the responsiveness of the afferent arteriole to angiotensin II by uncovering a potent constrictor response.

In summary, the renal effects of adenosine are very complex, but more and more data are accumulating indicating that this metabolite may be a very important regulator of renal vascular tone.

### *Prostaglandins*

While the role of prostaglandins in the control of basal or resting blood flow is felt to be insignificant [62] prostaglandins do seem to play a role as modulators of the renal vascular effects of a number of vasoconstrictor hormones [63].

The effect of blockade of renal prostaglandin synthesis depends on the level of activation of other neurohumoral vasoactive systems. In awake, sodium replete, unstressed animals, the administration of cyclooxygenase inhibitors has essentially no effect on renal blood flow or glomerular filtration rate [64]. However, in hypovolemic, anesthetized, or surgically operated animals, cyclooxygenase inhibition results in increased renal vascular resistance and decreased renal blood flow [64–66]. Situations where renal perfusion is reduced due to decreased intravascular volume or a fall in effective blood volume are associated with enhanced levels of angiotensin II, norepinephrine, and vasopressin. These neurohumoral agents have all been associated with increased renal prostaglandin synthesis [67–69]. Thus clinical conditions where prostaglandins may play an important role in modulating renal vascular resistance agents include anesthesia and surgical stress [66], renal ischemia [70], hemorrhagic hypotension [71], dehydration [71], congestive heart failure [72], and cirrhosis [73].

Prostaglandins may also play a role in augmenting the renal vasodilator response to other substances. Bradykinin, calcium ionophore, and furosemide augment renal $PGE_2$ synthesis which may contribute, in part, to the vasodilator actions of these agents [74–76].

During early ureteral obstruction, renal $PGE_2$ production is increased and contributes to the vasodilation seen [77]. The later stages of ureteral obstruction are characterized by vasoconstriction and increased levels of renal thromboxane $A_2$ synthesis [77].

The administration of prostaglandin inhibitors does not alter renal blood flow autoregulation [78].

In summary, it appears that prostaglandins act as local regulators of renal vascular tone. They contribute little to renal blood flow control in the resting state, but act to attenuate the renal vascular response to a variety of vasoconstrictor substances.

### *Kinins*

Bradykinin is the kinin released from plasma kallikrein. Infusion of the kinin in dogs [79], normal human subjects [80], or isolated perfused kidneys [81] result in marked renal vasodilatation. In isolated rabbit renal arterioles preconstricted with norepinephrine, bradykinin caused a dose-dependent relaxation of efferent arterioles with no effect on afferent arterioles [82].

A number of interactions has been described between the kallikrein-kinin system, the renin-angiotensin system and prostaglandins that may influence the effect of the kinins on renal blood flow. In the rat, aldosterone appears to stimulate kal-

likrein synthesis and secretion [83]. There is also some evidence that angiotensin II may stimulate renal kallikrein release [84]. Prostaglandins stimulate and prostaglandin synthesis inhibitors suppress renal kallikrein excretion [85]. Conversely, kinins stimulate prostaglandin production by perfused dog and rabbit kidneys [86, 87] and by blood vessels, including the renal artery and renal microvessels [88–90].

Despite extensive work, the physiologic role of kinins as regulators of renal blood flow remains to be clarified.

### *Atrial natriuretic peptide*

Recently, a family of endogenous peptides with diuretic, natriuretic, and vascular smooth muscle relaxant properties has been identified [91]. These peptides are released primarily from the cardiac atria in response to volume expansion and have been suggested to play a role in the control of sodium balance [92].

ANP has been demonstrated to relax both nonvascular smooth muscle and a variety of isolated vascular segments, including the renal artery [93–95]. In both conscious and anesthetized dogs, exogenous infusions of ANP have been consistently reported to produce an increase in renal blood flow, although this increase is frequently transient [96, 97]. Whole kidney filtration fraction showed consistent increases in both in vivo [96, 98] and in vitro studies [99, 100]. In isolated canine glomeruli perfused in vitro at constant pressure, infusion of ANP produced significant increases in single nephron glomerular filtration rate, single nephron filtration fraction, and glomerular capillary pressure, but no change in glomerular flow [100]. This is consistent with ANP-induced efferent arteriolar vasoconstriction with or without afferent arteriolar vasodilation. Yet, in rabbit superficial afferent and efferent arterioles, statically perfused in vitro, ANP had no effect on arteriolar lumen diameter both in the control state or in vessels preconstricted with norepinephrine or angiotensin II [101]. Further work is obviously needed in this intriguing area.

### *Endothelin*

As an example of the burgeoning field of new vasoactive agents, one only has to look at endothelin. This compound was first described in 1988 [102] and since has taken on a life of its own. It is an extraordinarily potent vasoconstrictor which can cause a marked decline in glomerular filtration rate and renal plasma flow and a reduction in the ultrafiltration coefficient [103]. In some model systems, it can stimulate prostacyclin [104], endothelial-derived relaxing factors such as nitric oxide [104], and atrial natriuretic peptide [105], while at the same time markedly reducing renin release [106]. Studies have clearly suggested that this agent may be involved in the pathophysiology of acute renal failure and, in fact, intrarenal infusion of an anti-endothelin antibody markedly attenuates the reduction in single nephron GFR observed after renal ischemia [107]. Thus, we have another peptide which may in fact be involved in the regulation of renal vascular tone.

## Conclusion

Every important regulatory system has an array of forces that may come into play to maintain homeostatic balance. This is certainly true of the renal circulation which may explain, at least in part, why Donald Seldin loves so much to talk about it.

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## References

1. Hura C, Stein JH: The renal circulation, in *Renal Physiology. Handbook of Physiology*, edited by G. Giebisch, E. Windhager (in press)
2. Brenner BM, Troy JL, Daugharty TM, Deen WM, Robertson CR: Dynamics of glomerular ultrafiltration in the rat. II. Plasma-flow dependence of GFR. *Am J Physiol* 223:1184–1190, 1972
3. Blantz RC: Effect of mannitol on glomerular ultrafiltration in the hydropenic rat. *J Clin Invest* 54:1135–1143, 1974
4. Robertson CR, Deen WM, Troy JL, Brenner BM: Dynamics of glomerular ultrafiltration in the rat. III. Hemodynamics and autoregulation. *Am J Physiol* 223:1191–1200, 1972
5. Navar LG: Minimal pre-glomerular resistance and calculation of normal glomerular pressure. *Am J Physiol* 219:1658–1664, 1970
6. Navar LG, Bungorn C, Bell PD: Absence of estimated glomerular pressure autoregulation during interrupted distal delivery. *Am J Physiol* 229:1596–1603, 1975
7. Boknam L, Ericson AC, Aberg B, Ulfendahl HR: Flow resistance of the interlobular artery in the rat kidney. *Acta Physiol Scand* 111:159–164, 1981
8. Navar LG, Bell PD, Burke TJ: Role of a macula densa feedback mechanism as a mediator of renal autoregulation. *Kidney Int* 22(Suppl 12):S-157–S-164, 1982
9. Blantz RC, Rector FC Jr, Seldin DW: Effect of hyperonecrotic albumin expansion upon glomerular ultrafiltration in the rat. *Kidney Int* 6:209–221, 1974
10. Myers BD, Deen WM, Brenner BM: Effects of norepinephrine and angiotensin II on the determinants of glomerular ultrafiltration and proximal tubule fluid reabsorption in the rat. *Circ Res* 37:101–110, 1975
11. Young DK, Marsh DJ: Pulse wave propagation in rat renal tubules: Implications for GFR and autoregulation. *Am J Physiol* 240 (Renal Fluid Electrol Physiol 9):F446–F458, 1981
12. Thurau K, Schnermann J: Die natriumkonzentration an den macula densa-zellen als regulierender Faktor fur das Glomerulumfiltrat. (mikropunktiorsversuche). *Klin Wochenschr* 43:410–413, 1965
13. Kallskog O, Lindbom LO, Ulfendahl HR, Wolgast M: Hydrostatic pressures within the vascular structures of the rat kidney. *Pflügers Arch* 363:205–210, 1976
14. Bayliss WM: On the local reactions of the arterial wall to changes in internal pressure. *J Physiol* (Lond) 28:220–226, 1902
15. Thurau K, Kramer K: Wertere untersuchungen zur myogen nature der autoregulation des nerenkreisllaufes. *Arch Ges Physiol* 269:77–85, 1959
16. Gilmore JP, Cornish KG, Rogers SD, Joyner WL: Direct evidence for myogenic autoregulation of the renal microcirculation in the hamster. *Circ Res* 47:226–230, 1980
17. Edwards RM: Segmental effects of norepinephrine and angiotensin II on isolated renal microvessels. *Am J Physiol* 244: (Renal Fluid Electrol Physiol 13):F526–F534, 1983
18. Hollenberg NK, Solomon HS, Adams DF, Abrams HL, Merrill JP: Renal vascular responses to angiotensin and norepinephrine in normal man. *Circ Res* 31:750–757, 1972
19. Cannon PJ, Ames RP, Laragh JH: Indirect action of angiotensin infusion to inhibit renal tubular sodium reabsorption in dogs. *Am J Physiol* 211:1021–1030, 1966
20. Porush JG, Kaloyanides GJ, Cacciaguida RJ, Rosen SM: The effects of angiotensin II and renal water and electrolyte excretion in normal and caval dogs. *J Clin Invest* 46:2109–2122, 1967

21. LOHMEIER TE, COWLEY AW: Hypertensive and renal effects of chronic low level intrarenal angiotensin infusion in the dog. *Circ Res* 44:154–160, 1979
22. ROSIVALL L, NAVAR LG: Effects on renal hemodynamics of intra-arterial infusions of angiotensins I and II. *Am J Physiol* 245 (Renal Fluid Electrol Physiol 14):F181–F187, 1983
23. BLANTZ RC, KONNEN KS, TUCKER BJ: Angiotensin II effects upon the glomerular microcirculation and ultrafiltration coefficient of the rat. *J Clin Invest* 57:419–434, 1976
24. ICHIKAWA I, MIELE JF, BRENNER BM: Reversal of renal cortical actions of angiotensin II by verapamil and manganese. *Kidney Int* 16:137–147, 1979
25. BROOKS VL, BROWNFIELD MS, REID IA: Measurement and localization of angiotensin like immunoreactivity in juxtaglomerular cells of the rat. *Regul Pept* 4:317–324, 1982
26. CELIO MR, INAGAMI T: Angiotensin II immunoreactivity coexists with renin in the juxtaglomerular granular cells of the kidney. *Proc Natl Acad Sci USA* 78:3897–3900, 1981
27. CALDWELL PRB, SEEGAL BC, HSU KC: Angiotensin coverting enzyme: Vascular endothelial localization. *Science* 191:1050–1051, 1976
28. ERDOS EG: The angiotensin I converting enzyme. *Fed Proc* 36:1760–1765, 1977
29. BRITTON SL: Intrarenal vascular effects of angiotensin I and angiotensin II. *Am J Physiol* 240 (Heart Circ Physiol 9):H914–H919, 1981
30. DISALVO J, PETERSON A, MONTEFUSCO C, MENTA M: Intrarenal conversion of angiotensin I to angiotensin II in the dog. *Circ Res* 29:398–406, 1971
31. FRANKLIN WG, PEACH MJ, GILMORE JP: Evidence for the renal conversion of angiotensin I in the dog. *Circ Res* 27:321–324, 1970
32. BAILIE MD, BARBOUR JA: Effect of inhibition of peptidase activity on distribution of intrarenal blood flow. *Am J Physiol* 228:850–853, 1975
33. HOISE KF, BROWN JJ, HARPER AM, LEVER AF, MACADRAM RF, MCGREGOR I, ROBERTSON JIS: The release of renin into the renal circulation of the anesthetized dog. *Clin Sci* 38:157–174, 1970
34. HORKY K, ROZO-ORTEGA JM, RODRIGUEZ N, BOUCHER R, GENEST J: Renin, renin-substrate and angiotensin I-converting enzyme in blood of rats. *Am J Physiol* 220:307–311, 1971
35. ANRENDSHORST WJ, FINN WF: Renal hemodynamics in the rat before and during inhibition of angiotensin II. *Am J Physiol* 233: (Renal Fluid Electrol Physiol 2) F290–297, 1977
36. HALL JE, GUYTON AC, SMITH MJ, COLEMAN TG: Chronic blockade of angiotensin II formation during sodium deprivation. *Am J Physiol* 237 (Renal Fluid Electrol Physiol 6):F424–F432, 1979
37. NAVAR LG, JIRAKULSOMCHOK D, BELL PD, THOMAS CE, HUANG WC: Influence of converting enzyme inhibition on renal hemodynamics and glomerular dynamics in sodium restricted dogs. *Hypertension* 4:58–68, 1982
38. ABE Y, KISHIMOTO T, YAMAMOTO K: Effect of angiotensin II antagonist infusion on autoregulation of renal blood flow. *Am J Physiol* 231:1267–1271, 1976
39. HALL JE, GUYTON AC, COWLEY AW JR: Dissociation of renal blood flow and filtration rate autoregulation by renin depletion. *Am J Physiol* 232 (Renal Fluid Electrol Physiol 1):F215–F221, 1977
40. GAGNON JA, KELLER HI, KOKOTIS W, SCHRIER RW: Analysis of role of renin-angiotensin system in autoregulation of glomerular filtration. *Am J Physiol* 219:491–496, 1970
41. STEINHAUSEN M, SNOEI H, PAREKH N, BAKER R, JOHNSON PC: Hydronephrosis: A new method to visualize vas afferens, efferens, and glomerular network. *Kidney Int* 23:794–806, 1983
42. STEINHAUSEN M, STERZEL RB, FLEMING JT, KUHN R, WEIS S: Acute and chronic effects of angiotensin II on the vessels of the split hydronephrotic kidney. *Kidney Int* (Suppl 20) 31:S-64–S-73, 1987
43. CARMNINES PK, MORRISON TK, NAVAR LG: Angiotensin II effects on microvascular diameters of in vitro blood-perfused juxtamedullary nephrons. *Am J Physiol* 251 (Renal Fluid Electrol Physiol 20):F610–F618, 1986
44. BENELLI G, DELLABELLA D, GANDINI A: Angiotensin and sympathetic nerve activity. *Br J Pharmacol* 22:211–219, 1964
45. ZIMMERMAN BG, GISSLEU G: Patterns of renal vasoconstriction and transmitter release during sympathetic stimulation in the presence of angiotensin and cocaine. *J Pharmacol Exp Ther* 163:320–329, 1968
46. KOPP UC, DIBONA GF: Interaction between neural and nonneural mechanisms controlling renin secretion rate. *Am J Physiol* 246 (Renal Fluid Electrol Physiol 15):F620–F626, 1984
47. HALL JE, GRANGER JP, HESTER RL: Interactions between adenosine and angiotensin II in controlling glomerular filtration. *Am J Physiol* 248 (Renal Fluid Electrol Physiol 17):F340–F346, 1985
48. HALL JE, GRANGER JP: Adenosine alters glomerular filtration control by angiotensin II. *Am J Physiol* 250 (Renal Fluid Electrol Physiol 19):F917–F923, 1986
49. ICHIKAWA I, BRENNER BM: Evidence for glomerular actions of ADH and dibutyryl cyclic AMP in the rat. *Am J Physiol* 233:F102–F117, 1977
50. OLIVER JA, SCIACCA RR, LECREN G, CANNON PJ: Modulation by prostaglandins of the renal vascular action of arginine vasopressin. *Prostaglandins* 24(5):641–655, 1982
51. SCHMID PG, ABBOUD FM, WENDLING MG, RAMBERG ES, MARK AL, HEISTAD DD, ECKSTEIN JW: Regional vascular effects of vasopressin: Plasma levels and circulatory responses. *Am J Physiol* 227:998–1004, 1974
52. BUNAG RD, PAGE IH, MCCUBBIN JW: Inhibition of renin release by vasopressing and angiotensin. *Cardiovasc Res* 1:67–73, 1967
53. FOURMAN J, KENNEDY GC: An effect of antidiuretic hormone on the flow of blood through the vasa recta of the rat kidney. *J Endocrinol* 35:173–176, 1966
54. THURAU K, DEETJEN P, KRAMER K: Hamodynamik des nierenmarks. II. mitteilung, *Pflügers Arch* 270:270–285, 1960
55. ZIMMERHACKL B, ROBERTSON CR, JAMISON RL: Effect of arginine vasopressin on renal medullary blood flow. *J Clin Invest* 76:770–778, 1985
56. SPIELMAN WS, THOMPSON CI: A proposed role for adenosine in the regulation of renal hemodynamics and renin release. *Am J Physiol* 242 (Renal Fluid Electrol Physiol 11):F423–F435, 1982
57. OSSWALD H, SPIELMAN WS, KNOX FG: Mechanisms of adenosine-mediated decreases in glomerular filtration rate in dogs. *Circ Res* 43:465–469, 1978
58. HALL JE, GRANGER JP: Renal hemodynamics and arterial pressure during chronic intrarenal adenosine infusion in conscious dogs. *Am J Physiol* 250 (Renal Fluid Electrol Physiol 19):F32–F39, 1986
59. TAGAWA H, VANDER AJ: Effects of adenosine compounds on renal function and renin secretion in dogs. *Circ Res* 26:327–338, 1970
60. HURA C, TAMAKI T, KUNAU RT JR: Prostaglandins as modulators of the vasoconstrictor effect of 2-chloroadenosine in isolated canine afferent arterioles. (abstract) *Kidney Int* 31:423, 1987
61. AREND LJ, THOMPSON CI, SPIELMAN WS: Dipyridamole decreases glomerular filtration in the sodium-depleted dog. *Circ Res* 56:242–251, 1985
62. DUNN MJ, HOOD VL: Prostaglandins and the kidney. *Am J Physiol* 233 (Renal Fluid Electrol Physiol 2):F169–F184, 1977
63. DUNN MJ, ZAMBRASKI EJ: Renal effects of drugs that inhibit prostaglandin synthesis. *Kidney Int* 18:609–622, 1980
64. BLASINGHAM MC, NASILETTI A: Differential renal effects of cyclooxygenase inhibition in sodium-replete and sodium-deprived dog. *Am J Physiol* 239 (Renal Fluid Electrol Physiol 8):F360–F365, 1980
65. KIRSCHENBAUM MA, STEIN JH: The effect of inhibition of prostaglandin synthesis on urinary sodium excretion in the conscious dog. *J Clin Invest* 57:517–521, 1976
66. TERRAGNO NA, TERRAGNO A, MCGIFF JC: Contribution of prostaglandins to the renal circulation in conscious, anesthetized and laparotomized dogs. *Circ Res* 40:590–595, 1977
67. LIEBERTHAL W, LEVINE L: Stimulation of prostaglandin production in rat glomerular epithelial cells by antidiuretic hormone. *Kidney Int* 25:766–770, 1984
68. MCGIFF JC, CROWSHAW K, TERRAGNO NA, LONIGRO AJ: Release of a prostaglandin-like substance into renal venous blood in

response to angiotensin II. *Circ Res* 26-27 (Suppl I):I121–I130, 1970
69. NEEDLEMAN P, DOUGLAS JR, JAKSCHIK B, STOEKLIN PB, JOHNSON EM: Release of renal prostaglandin by catecholamines: Relationship to renal endocrine function. *J Pharmacol Exp Ther* 188:453–460, 1974
70. DUNN MJ, LIARD JF, DRAY F: Basal and stimulated rates of renal secretion and excretion of prostaglandins $E_2$, F and 13-14 dihydro-15-keto-F2. *Kidney Int* 13:136–143, 1978
71. HENRICH WL, ANDERSON RJ, BERNS AS, MCDONALD KM, PAULSEN PJ, BERL T, SCHRIER RW: The role of renal nerves and prostaglandins in control of renal hemodynamics and plasma renin activity during hypotensive hemorrhage in the dog. *J Clin Invest* 61:744–750, 1978
72. OLIVER JA, SCIACCA RR, PINTO J: Participation of the prostaglandins in the control of renal blood flow during acute reduction of cardiac output in the dog. *J Clin Invest* 67:229–237, 1981
73. BOYER TD, REYNOLDS TB: Prostaglandin insufficiency. A role in the hepatorenal syndrome. (abstract) *Gastroenterol* 71:899, 1976
74. BLASINGHAM MC, NASJLETTI A: Contribution of renal prostaglandins to the natriuretic action of bradykinin in the dog. *Am J Physiol* 237 (Renal Fluid Electrol Physiol 6):F182–F187, 1979
75. OKAHARA T, ABE Y, IMANISHI M: Effects of calcium ionophore A23187 on prostaglandin $E_2$ and renin release in dogs. *Jap Circ J* 44:394–399, 1980
76. PATAK RV, FADEM SZ, ROSENBLATT SG, LIFSCHITZ MD: Diuretic induced changes in renal blood flow and prostaglandin E excretion in the dog. *Am J Physiol* 236 (Renal Fluid Electrol Physiol 5):F494–F500, 1979
77. CURRIE M, KAWASAKI A, JONAS P, DAVIS B, NEEDLEMAN P: The mechanism and site of enhanced arachidonate metabolism in ureter obstruction, in *Prostaglandins and the Kidney*, edited by MJ DUNN, C PATRONO, GA CINOTTI, New York, Plenum Press, 1983, pp. 299–308
78. VENUTO R, O'DORISIO CT, FERRIS TF, STEIN JH: Prostaglandins and renal function II. The effect of prostaglandin inhibition on autoregulation of blood flow in the intact kidney of the dog. *Prostaglandins* 9:817–828, 1975
79. STEIN JH, CONGBALAY RC, KARSH KL, OSGOOD RW, FERRIS TF: The effect of bradykinin on proximal tubular sodium reabsorption in the dog. Evidence for functional nephron heterogeneity. *J Clin Invest* 51:1709–1721, 1972
80. GILL JR, MELMON KL JR, GILLESPIE L, BARTTER FC JR: Bradykinin and renal function in normal man: Effects of adrenergic blockade. *Am J Physiol* 209:844–848, 1965
81. MCGIFF JC, ITSKOVITZ HD, TERRAGNO NA: The actions of bradykinin and eledoisin in the canine isolated kidney: Relationships to prostaglandins. *Clin Sci Mol Med* 49:125–131, 1975
82. EDWARDS RM: Response of isolated renal arterioles to acetylcholine, dopamine, and bradykinin. *Am J Physiol* 248 (Renal Fluid Electrol Physiol 17):F183–F189, 1985
83. MARGOLIUS HS, CHAO J, KAIZU T: The effects of aldosterone and spironolactone on renal kallikrein in the rat. *Clin Sci Mol Med* 51:279s–282s, 1976
84. MARGOLIUS HS, HORWTIZ D, GELLER RB, ALEXANDER RW, GILL JR, PISANO JJ, KEISER HR: Urinary kallikrein excretion in normal man. Relationships to sodium intake and solium-retaining steroids. *Circ Res* 35:812–819, 1974
85. NASJLETTI A, MALIK KU: Relationships between the kallikrein-kinin and prostaglandin system. *Life Sci* 25:99–110, 1979
86. COLINA-CHOURIO J, MCGIFF JC, MILLER NP, NASJLETTI A: Possible influence of intrarenal generation of kinins prostaglandin release from the rabbit perfused kidney. *Br J Pharmacol* 58:165–172, 1976
87. MCGIFF JC, TERRAGNO NA, MALIK KU, LONIGRO AJ: Release of prostaglandin E-like substance from canine kidney by bradykinin. *Circ Res* 31:36–43, 1972
88. BLUMBERG AL, DENNY SE, MARSHALL GR, NEEDLEMAN P: Blood vessel hormone interactions: Angiotensin, bradykinin, and prostaglandins. *Am J Physiol* 232 (Heart Circ Physiol 1):H305–H310, 1977
89. SATOH H, HOSONO M, SATOH S: Distinctive effect of angiotensin II on prostaglandin production in dog renal and femoral arteries. *Prostaglandins* 27:807–820, 1984
90. HURA CE, KUNAU RT: Prostaglandin production by isolated renal afferent arterioles. *Am J Physiol* 254 (Renal Fluid Electrol Physiol 23):F734–F738, 1988
91. THIBAULT G, LAZURE C, SCHIFFRIN EL, GUTKOWSKA J, CHARTIER L, GARCIA R, SEIDAH NG, CHRETIEN M, GENEST J, CANTIN M: Identification of a biologically active circulating form of rat atrial natriuretic factor. *Biochem Biophys Res Commun* 130:981–986, 1985
92. NEEDLEMAN P, ADAMS SP, COLE BR, CURRIE MG, GELLER DM, MICHENER ML, SAPER CB, SCHWARTZ D, STANDAERT DG: Atriopeptins as cardiac hormones. *Hypertension* 7:469–482, 1985
93. CAMARGO MJF, KLEINERT HD, ATLAS SA, SEALEY JE, LARAGH JE, MAACK T: Ca-dependent hemodynamic and natriuretic effects of atrial extract in isolated rat kidney. *Am J Physiol* 246 (Renal Fluid Electrol Physiol 15):F447–F456, 1984
94. CURRIE MG, GELLER DM, COLE BR, BOYLAN JE, YUSHENG W, HOLMBERG SW, NEEDLEMAN P: Bioactive cardiac substances: Potent vasorelaxant activity in mammalian atria. *Science* 221:71–73, 1983
95. KLEINERT HD, MAACK T, ATLAS SA, JANUSZEWICZ J, SEALEY JE, LARAGH JH: Atrial natriuretic factor inhibits angiotensin-, norepinephrine-, and potassium-induced vascular contractility. *Hypertension* 6 (Suppl I):I-143–I-147, 1984
96. BURNETT JC, GRANGER JP, OPGENORTH TJ: Effects of synthetic atrial natriuretic factor on renal function and renin release. *Am J Physiol* 247 (Renal Fluid Electrol Physiol 16):F863–F866, 1984
97. HINTZE TH, CURRIE MG, NEEDLEMAN P: Atriopeptins: Renal specific vasodilators in conscious dogs. *Am J Physiol* 248 (Heart Circ Physiol 17):H587–H591, 1985
98. BEASLEY P, MALVIN RL: Atrial extracts increase glomerular filtration rate in vivo. *Am J Physiol* 248 (Renal Fluid Electrol Physiol 17):F24–F30, 1984
99. MURRAY RD, ITOH S, INAGAMI T, MISONO K, SETO S, SCICLI AG, CARRETERO DA: Effects of synthetic atrial natriuretic factor in the isolated perfused rat kidney. *Am J Physiol* 249 (Renal Fluid Electrol Physiol 18):F603–F609, 1985
100. FRIED TA, MCCOY RN, OSGOOD RW, STEIN JH: The effect of atriopeptin II on determinants of glomerular filtration rate in the in-vitro perfused dog glomerulus. *Am J Physiol* 250: (Renal Fluid Electrol Physiol 19):F1119–F1122, 1986
101. EDWARDS RM, WEIDLEY EF: Lack of effect of atriopeptin II on rabbit glomerular arterioles in vitro. *Am J Physiol* 252 (Renal Fluid Electrol Physiol 21):F317–F321, 1987
102. YANAGISAWA M, KURIHARA H, KIMURA S, TOMOBE Y, KOBAYASHI M, MITSUI Y, YAZAKI Y, GOTO K, MASAKI T: A novel potent vasoconstrictor peptide produced by vascular endothelial cells. *Nature* (Lond) 332:411–415, 1988
103. KING AJ, BRENNER BM, ANDERSON S: Endothelin: A potent renal and systemic vasoconstrictor peptide. *Am J Physiol* 256: F1051–F1058, 1989
104. DENUCCI G, THOMAS R, D'ORLLEANS-JUST P, ANTUNES E, WALDER C, WARNER TD, VANE JR: Pressor effects of circulating endothelin are limited by its removal in the pulmonary circulation and by the release of prostacyclin and endothelium-derived relaxing factor. *Proc Natl Acad Sci USA* 85:9797–9800, 1988
105. MILLER WL, REDFIELD MM, BURNETT JC JR: Integrated cardiac, renal, and endocrine actions of endothelin. *J Clin Invest* 83:317–320, 1989
106. TAGAKI M, MATSUOKA H, ATARASHI K, YAGI S: Endothelin: A new inhibitor of renin release. *Biochem Biophys Res Commun* 157:1164–1168, 1988
107. KON V, YOSHIOKA T, FOGO A, ICHIKAWA I: Glomerular actions of endothelin in vivo. *J Clin Invest* 83:1762–1767, 1989